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High Dose of Intravenous Antithrombin III Without Heparin in the Treatment of Disseminated Intravascular Coagulation and Organ Failure in Four Children

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In several animal experiments, high doses of antithrombin III concentrates have shown beneficial effects on mortality and reversal of coagulation abnormalities which had resulted from disseminated intravascular coagulation. Other experiments have suggested that antithrombin III infusion without heparin is effective in the treatment of organ failure. We clinically treated children suffering disseminated intravascular coagulation only with antithrombin concentrate. Four patients suffering disseminated intravascular coagulation with organ failure were selected. We started antithrombin III concentrate infusion as soon as the diagnosis was established. The dosage of antithrombin III was 120–250 units/kg/day for 2 or 3 days. Heparin was not used. All 4 patients recovered completely and quickly without any complications within 14 days. We suggest that the high-dose antithrombin III infusion without heparin is an effective and safe therapy for disseminated intravascular coagulation with organ failure. © 1996 Wiley-Liss, Inc.

Key words: pediatrics, shock, Reye syndrome, coagulation, multiple system organ failure

INTRODUCTION

Antithrombin III is a major inhibitor of blood coagulation through formation of complexes with activated clotting factors such as thrombin, and factors Xa, IXa, XIa, and XIIa. Heparin achieves an approximately 1,000-fold increase in the thrombin-inhibitory capacity of antithrombin III. Antithrombin III concentrates, heparin, and other blood products have long been used in combination in patients suffering with disseminated intravenous coagulation (DIC) [1–3]. We have often witnessed life-threatening bleeding during heparin infusion for treatment of DIC, and have long had grave doubts about the use of heparin in management of DIC. Several studies suggest a beneficial effect of using antithrombin III concentrates alone in DIC [1,4].

Mutliple system organ failure (MSOF), defined as the failure of at least two organ systems, includes DIC. The mortality rate for children with MSOF has been very high, and the overall mortality has been about 50% [5,6]. Effective therapy for MSOF has been sought.

Several DIC animal models demonstrated that high doses of antithrombin III concentrates attenuated organ damage and prevented death [7,8].

We defined DIC with organ failure as MSOF including DIC, and we used high-dose antithrombin III concentrates for children suffering DIC with organ failure.

PATIENTS AND METHODS (TABLE I)

We selected 4 consecutive children suffering DIC with organ failure from March 1994–August 1995 in two institutions as subjects. We treated each patient with a high dose of antithrombin III without heparin infusion or any other supportive therapy.

DIC was diagnosed by clinical symptoms and abnormal blood coagulation systems as follows: decreased platelet count, decreased plasma fibrinogen concentration, and

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TABLE I. Patient Profiles*

Case no.	1	2	3	4
Age/sex, diagnosis	8 months/male, Reye syndrome, DIC, OFs	1 year, 5 months/female, Down's syndrome, VSD, post op, DIC, OF	3 months/male, SRV, PS, post op, shock, DIC, OF	20 days/male, HLHS shock, DIC, OF
Laboratory data				
AST, U/l	14,300	373	218	739
ALT, U/l	5,460	164	55	134
LDH, U/l	45,550	1,866	3,294	3,640
CK, U/l	450	17,140	1,574	1,175
Amylase, U/l	295			25
UN, mg/dl	42.6	35.6	25	8
Cr, mg/dl	1.3	0.5	0.7	1.3
WBC $\times 10^3/\mu l$	5.9	11.7	8.2	21.9
RBC $\times 10^6/\mu l$	4.13	3.74	3.43	3.37
PLT $\times 10^4/\mu l$	9.8	4.0	18.1	6.8
PT (%)	22.7	61.3	44.2	
aPTT, sec	48	89	85	
Fibrinogen, mg/dl	146	148	144	71
Antithrombin III (%)		50	40	23
FDP, μg/ml	168	27		<40
D-dimer, μg/ml	105		37	
Treatment				
Antithrombin III, U/kg/day	120 for 3 days	200 for 2 days	150 for 2 days	250 for 3 days
Other	Exchange transfusion	Gabexate mesilate		
Posttreatment	Nafamostat mesilate			
Antithrombin III (%)	<130	<130	113	180
Period of recovery	14 days	14 days	8 days	8 days

*Table shows diagnosis, laboratory data at onset, treatment method, and period of recovery. AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; UN, urea nitrogen; Cr, creatinine; WBC, white blood cell count; RBC, red blood cell count; PLT, platelet count; PT, prothrombin time; aPTT, activated partial thrombin time; FDP, fibrin-fibrinogen degradation products.

increased fibrin-fibrinogen degradation products and/or D-dimer. Organ failure was diagnosed by abnormal blood chemistry data as follows: aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, amylase, urea nitrogen, and creatinine. Blood cell counts, blood chemistry, and blood coagulation assay were performed by standard laboratory techniques. We started antithrombin III concentrate infusion as soon as the diagnosis of DIC with organ failure was established. The dosage of antithrombin III was 120–250 units/kg/day for 2 or 3 days. Heparin was not used. Informed consent was obtained from the patients' parents.

Subjects

Case 1. An 8-month-old boy with drowsiness and hypotension came to our hospital. He had had a high fever of over 40°C and frequent watery diarrhea for 2 days. Chest X-ray and electrocardiography were within normal limits. DIC with multiple organ failure was diagnosed by laboratory data. Antithrombin III concentrate (120 units/kg/day) was administered for 3 days. Altogether, he was treated by means of continuous infusion of nafamostat mesilate for 7 days, and once with exchange transfusion and other nonspecific supportive therapies, including continuous infusion of dobutamine. A liver biopsy on day 6 revealed he had a fatty liver, so he was diagnosed with DIC with organ failure triggered by Reye syndrome.

Case 2. A 1-year-and-5-month-old girl with 21-trisomy, ventricular septal defect, and pulmonary hypertension successfully received a patch closure of the ventricular septal defect. Echocardiography revealed that her ventricular function was within normal limits and that she had no pulmonary hypertension. The day after surgery she appeared to be recovering comfortably in the oxygen tent. However, after 3 days, her temperature rose to over 40°C and she developed frequent convulsions that were difficult to control over 3 days. Table I shows her laboratory data. We diagnosed her state as DIC with liver dysfunction triggered by open-heart surgery. Antithrombin III concentrate (200 units/kg/day) was administered for 2 days; she was also treated with continuous infusion of gabexate mesilate for 7 days and other nonspecific supportive therapies.

Case 3. A 3-month-old boy was diagnosed with single right ventricle, d-malposition of the great arteries and pulmonary stenosis after a shunt operation from the descending aorta to the left pulmonary artery. He suddenly went into shock associated with apnea, bradycardia, and hypotension, after crying severely. He was immediately resuscitated by artificial respiration and infusion of bicar-

bonates because of severe acidosis: pH 6.99, PCO_2 27.7 mm Hg, PO_2 153 mm Hg, base excess −24.5 mEq/l. He recovered quickly from his shock and resumed normal activity, but the next day, he suffered frequent watery diarrhea. Table I shows his laboratory data. We diagnosed his state as DIC with liver and intestinal dysfunction triggered by cardiocirculatory failure. We administered antithrombin III at 150 units/kg/day for 2 days along with other supportive therapies, but used neither heparin nor protease inhibitors.

Case 4. A 20-day-old boy was diagnosed with hypoplastic left heart syndrome after undergoing mechanical respiration for 14 days because of respiratory distress. He was administered lipoprostaglandin E1 continuously in an attempt to prevent ductal closure, but he developed systemic hypotension (45/25 mm Hg), anuria, and lung congestion. His blood gas analysis showed severe metabolic acidosis as follows: pH 6.98, PCO_2 17.3 mm Hg, PO_2 69.5 mm Hg, base excess −27.5 mEq/l. He was immediately administrated bicarbonate and volume expanders, and he recovered systemic blood pressure and urine volume. After 6 hr, his laboratory data fit the definition of DIC with liver dysfunction (Table I) triggered by cardiocirculatory failure. We gave him antithrombin III at 250 units/kg/day for 3 days and applied other supportive therapies, but used neither heparin nor protease inhibitors.

RESULTS

All 4 patients recovered completely and resumed normal activity. Laboratory data (blood cell counts, blood chemistry, and blood coagulation) also became normal within 14 days. Peak plasma antithrombin levels after administration were over 130% of normal (cases 1 and 2), 113% of normal (case 3), and 180% of normal (case 4). There was no bleeding tendency such as gastrointestinal or lung bleeding, in spite of the supernormal plasma antithrombin III levels. There were no other complications during or after treatment.

DISCUSSION

Treatment of DIC has been by three methods: heparin, heparin + antithrombin III substitution, and antithrombin III substitution alone. Treatment by heparin infusion has a potential risk of severe hemorrhagic complications when the dose of heparin is more than appropriate [9]. A randomized study of DIC treatments that included heparin, antithrombin III substitution, or a combination of both substances, demonstrated that heparin and combination treatments reduced the platelet count, while antithrombin substitution treatment shortened the duration of symptoms of DIC [1]. Antithrombin III is seriously involved in consumption of antithrombin III with the development of DIC. Therefore, antithrombin III substitution may be of therapeutic benefit to the patient [4].

Several recent animal experiments, using 10–15 times the pretreatment high dose of antithrombin III alone (100–250 units/kg), have shown beneficial prophylactic effects on mortality and restoration of coagulation abnormalities resulting from DIC and/or MSOF [7,8]. The mechanisms of the beneficial effects on DIC are unknown. Several reports, however, speculate that DIC associated with organ failure involves both microthrombus formation and injury of endothelial cells and organs by cytokines induced by activated monocytes and polymorphonuclearleukocytes; each of these exacerbates the other [10–12].

DIC with organ failure as induced by several diseases is a lethal state without appropriate therapy. Despite the fact that the majority of patients dying in the pediatric intensive care unit have features of MSOF, there are very few publications concerning children with MSOF. Higher mortality rate (>50%), in spite of intensive care, has been reported with an increased number of simultaneous organ failures [5,6]. We therefore sought an effective therapy for DIC with organ failure.

Based on the above considerations, we attempted treatment with high doses of antithrombin III in children suffering DIC with organ failure triggered by Reye syndrome (case 1), open-heart surgery (case 2), and cardiocirculatory failure (cases 3 and 4). DIC with organ failure triggered by these diseases has high mortalities (42% [13], 43% [14], and 27% [15]) and high rates of sequelae. In comparison with these figures, we observed that high-dose antithrombin III treatment had excellent clinical effects. Patient management with this method was easier than with heparin, since patients were less likely to bleed in the gastrointestinal tract or lung. The peak plasma antithrombin III concentration was 113–180% of normal the day after the last infusion, but these high concentrations appear not to have caused any complications. We therefore recommend high-dose antithrombin III infusion without heparin as a safe therapy for DIC with organ failure.

The timing of onset of antithrombin III administration could be a pivotal factor; we started infusion as soon as the diagnosis of DIC was established, because high-dose antithrombin III treatment had shown only prophylactic effects in animal experiments [7,8]. The per-day dosages of antithrombin III concentrates were 3–6 times the usual, and were continued for 2 or 3 days. Infusion times were 1–2 hr in order to avoid volume overload.

Study Limitations

The patient number was small in this study. We will report further results with this method as cases of this rare disorder are referred for treatment in the future.

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